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EXAMINER
WEGERT, SANDRA L

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,927	ZON ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-133* is/are pending in the application.

4a) Of the above claim(s) *1-45 and 73-133* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-133* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Information Disclosure Statement received 6/18/01 (Paper 5) has been entered into the record. Applicant's election of Invention I, (claims 1-72) in Paper No. 10 is acknowledged. In addition, Applicant elected: SEQ ID NO: 5 and 7.

The Applicant traversed the first restriction and argued that the claims of Invention V and VII should be rejoined. Applicant argues that Invention VII simply adds more steps to Invention V. However, the claims of Invention V and the claims of Invention VII were restricted properly, because the methods of Invention V and the methods of Invention VII are independent and distinct in that they are practiced with materially different process steps for materially different purposes and each method requires a non-coextensive search because of different starting materials, process steps, and goals. The method of Invention V is an *in vitro* method comprising using cultured cells to measure iron flux in the presence of another agent. The culture comprises *one* type of cell, either known to express the transporter or transfected with polynucleotides encoding the iron transporter. Concentrations of added antagonists can be easily measured, as can iron transport. However, the method of Invention VII is an *in vivo* method comprising using animals to measure transport of exogenously-supplied iron, after administration of an inhibitor. The methods are very different from those used with cultured cells. Several organs and cell types may be involved in iron transport in animals. The concentrations of inhibiting agents bathing the various cells and the concentrations of iron can be

only inferred indirectly, for example: from concentrations in bodily fluids. Furthermore, since Invention VII also comprises a method of treatment, the experimenters will also be concerned with animal physiology and metabolism, possible identification and diagnosis of disease, drug side effects and drug doses.

Similarly, applicant also traversed the restriction between Inventions IX and XI and argued that the claims of Inventions IX and XI should be rejoined. However, the claims of Invention IX and the claims of Invention XI were restricted properly, because the methods of Invention IX and Invention XII are independent and distinct in that they are practiced with materially different process steps for materially different purposes and each method requires a non-coextensive search because of different starting materials (e.g., cells vs animals), process steps, and goals. The method of Invention IX is an *in vitro* method comprising using cultured cells to measure iron flux in the presence of another agent. The culture comprises *one* type of cell, either known to express the transporter or transfected with polynucleotides encoding the iron transporter. Concentrations of added agonists can be easily measured, as can iron transport. The method of Invention XI is an *in vivo* method comprising the use of multicellular animals to measure transport of exogenously-supplied iron after administration of an agonist. The methods are very different from those used with cultured cells. The goals of each invention are very different. Cell culture intrinsically has few variables. It would therefore be useful for studying the transduction processes of transfected transporters under precisely-defined experimental conditions. Invention XI uses multicellular organisms, which themselves are highly variable. Additionally, it is not known which organs and tissues are involved in iron transport involving the Ferroportin1 transporter. Furthermore, since Invention XI also encompasses a method of

treatment, animal physiology and metabolism, identification and diagnosis of disease, drug side effects and drug doses must be taken into account.

The Applicant has pointed out that Claim 130 is found in two inventive Groups. As pointed out by the Applicant, Claim 130 does *not* encompass an enhancer of iron transport; therefore it should only be part of one Inventive Group. Applicant traversed the restriction of Claims 129 and 130, which is argued above in the discussion about the restriction between Inventions IX and XII. The method steps and goals of the two Inventions are different, and searching each Invention would constitute an undue burden.

Applicant also traversed the Restriction of a SEQ ID NO. However, the SEQ ID NO's were properly restricted because each sequence represents a patentably distinct invention. The sequences are independent and distinct, have different putative functions, have different structures, and require completely different search terms, starting points and strategies. Since the sequences are presumed to encode different polypeptides (unless they can be shown to be indistinguishable), searching all sequences together would constitute an undue burden.

Finally, the examiner agrees with the Applicant's request that the elected polynucleotides may be identified in terms of the polypeptide that they encode.

Claims 1-45 and 73-133 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claims.

Claims 46-72 are under examination in the Instant Application.

Informalities

Specification

The disclosure is objected to because of the following informalities:

URL's

The disclosure is objected to because it contains browser-executable code. This occurs, for example, on p. 55, in the first paragraph. All URL's should be removed from the Specification. Applicant may refer to web sites by non-executable name only. See MPEP § 608.01 (p).

Appropriate correction is required.

35 USC § 112, first paragraph-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 46-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleic acid encoding the Zebrafish ferroportin1 transporter (SEQ ID NO: 1), does not reasonably provide enablement for the nucleic acid(s) encoding the human

polypeptide of SEQ ID NO: 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a polynucleotide encoding a transporter polypeptide. The specification discloses a Zebrafish iron transporter and uses it to measure iron flux across Xenopus oocytes transfected with the polynucleotide(s) encoding the transporter. The specification also discloses methods for recombinantly expressing the disclosed transporter polypeptides. The specification further discloses human and mouse polypeptides that appear to have 9-12 transmembrane domains -typical of a transporter- and 82-89% similarity to the Zebrafish iron transporter. However, the scope of the patent protection sought by the Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons:

The specification discloses an enabled utility for the polypeptide encoded by the DNA of SEQ ID NO: 1, as to be used to transport iron across the plasma membrane of cells expressing or transfected with the polynucleotide. Since the transporter of SEQ ID NO: 1 is an iron *exporter* (see p. 59 and Fig. 3) it must be used in concert with an iron *importer* to facilitate measurement of iron flux across transfected cells. Applicants have demonstrated, using transfected Xenopus oocytes, that the polypeptide encoded by SEQ ID NO: 1 (SEQ ID NO: 2) is a transmembrane transporter. Furthermore, by performing the iron flux experiments in the presence and absence of an iron chelator, they have demonstrated that the transporter binds and translocates *iron* specifically. By further transfecting the cells with a known iron transporter that translocates iron *into* cells, they have shown that the Zebrafish ferroportin transports iron *out* of a cell.

However, the Applicants claim the transporter encoded by SEQ ID NO: 5 and 7, which bears 82% similarity to the Zebrafish transporter enabled by the instant Specification. There is no discussion, or working examples disclosed in the instant case, as to what amino acids are necessary to maintain the functional characteristics of the claimed polynucleotide(s), or to connect the function of the claimed human polypeptide of SEQ ID NO: 6 to that of the disclosed Zebrafish transporter of SEQ ID NO: 2. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to another protein. For example, Smith et al. (1997, Nature Biotechnology 15:1222-1223) demonstrate that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Additionally, the art shows that transporter families have members with high structural similarities but disparate functions. Bisson, *et al* (1993, Crit Rev Biochem Mol Biol, 28:259) studied yeast transporter knockout phenotypes, and found little correlation between homology and the substrate transported. For example, they found that yeast transporters *Gal2* and *Hxt4* displayed 83.7% homology, but *Gal2* appears to transport Galactose, while *Hxt4* appears to transport Glucose (based on knockout phenotype- compare Table 1 and Table 2A). Similarly, Liang et al found that several single amino acid substitutions in yeast glucose transporters can change substrate specificity (Liang, H., et al (1998) Mol. Cell. Biol. 18(2): 926). These examples and others demonstrate that it is not predictable as to which amino acids are necessary to maintain the functional characteristics of a protein.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Due to the large quantity of experimentation required to: determine how to use the polypeptide of SEQ ID NO: 6; the lack of direction or guidance in the specification regarding same (e.g., which amino acids are necessary to maintain the functional characteristics of the polypeptide encoded by the claimed polynucleotide(s) of SEQ ID NO: 5 and 7); the lack of working examples to the polypeptides encoded by SEQ ID NO: 5 and 7; and the state of the art showing the unpredictability of function based on structural similarity of transporter proteins, - undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Furthermore, the specification is not enabling for various forms of the polypeptide encoded by SEQ ID NO: 5 and 7, wherein the DNA sequence is at least 80% identical to the nucleic acid sequence(s) encoding SEQ ID NO: 6, as recited in claims 47, 54, 57, 60, 62 and 67. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are directed to a polynucleotide encoding a transporter polypeptide. The specification discloses mouse, human and Zebrafish transporters

The specification discloses the human transporter encoded by the DNA of SEQ ID NO: 5 and 7. However, there is no discussion, or working examples disclosed in the instant case, as to what amino acids are necessary to impart or maintain the functional characteristics of the claimed polynucleotide(s). The instant case claims altering as much as 10% of the polynucleotide encoding the polypeptide of SEQ ID NO: 6. However, as discussed above, the art shows that transporter families have members with high structural similarities but disparate functions. Therefore, it is not predictable as to which amino acids are necessary to maintain the functional characteristics of a protein.

For similar reasons, the specification is not enabling for various *fragments* of the polypeptide encoded by SEQ ID NO: 5 and 7, as recited in claims 49, 50, 58, 63, 64 and 68. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Claims 49, 50, 58, 63, 64 and 68 read on defined and undefined fragments of the polynucleotide(s) encoding SEQ ID NO: 6. However, the specific activities of the proteins encoded by the claimed nucleotide fragments are not disclosed. Nor are there disclosed assays to test for these activities. There is no discussion or working examples, disclosed in the instant case, as to what amino acids are necessary to maintain the functional characteristics of the polypeptide fragments encoded by the claimed polynucleotides.

Furthermore, the specification does not reasonably provide enablement for use of the polypeptide or polynucleotide *allelic variant* as recited in claim 51. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim. The

Applicants have not identified allelic variants of the Ferroportin1 protein recited in the claim, nor of the polypeptide encoded by SEQ ID NO: 5. Furthermore, the applicants have not precisely localized the gene to a particular locus of a chromosome. Claim 51 encompasses numerous undefined variants of SEQ ID NO: 5, without precise recitations of function that can be applied to allelic variants. Furthermore, as discussed above, it is not predictable as to which variants are tolerated while still maintaining the functional characteristics of a protein.

Due to the large quantity of experimentation required to: determine how to use all variants of SEQ ID NO: 5 and 7; the lack of direction or guidance in the specification regarding same - e.g., the lack of guidance regarding specific activity of SEQ ID NO: 5 and 7 as well as activity of the fragments of the polynucleotides; the lack of guidance regarding allelic variants of SEQ ID NO: 5; the lack of guidance as to polynucleotides that are at least 90% identical; the lack of working examples to all variants of SEQ ID NO: 5 and 7; the state of the art showing the unpredictability of function based on structural similarity of transporter polypeptides; and the breadth of the claims which embrace innumerable variants of SEQ ID NO: 5 and 7-- undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

35 USC § 102-Prior Art

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 55, 58, 64 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Fujiwara, et al (1995). Claims 55, 58, 64 and 68 read on a polynucleotide "portion", which can be any length. Therefore, the Fujiwara Clone falls within the scope of the claims of the instant application.

Conclusion:

Claims 46-72 are rejected for the reasons cited above.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:30 AM to 6:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623. Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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SLW

7/22/02